HIV and Cellular Factors

Kuan-Teh Jeang

Molecular Virology Section, LMM, NIAID, National Institutes of Health,
Bethesda, MD 20892-0460, USA

Introduction

Viruses are obligatory parasites of cells. Thus it is expected that host cell factors contribute importantly to the life-cycle of viruses. In this section, we survey, for HIV-1, four types of virus-cell interactions. These four areas include: 1) DNA-binding proteins that recognize target motifs in proviral LTR; 2) RNA-binding proteins that bind HIV-1 RNAs; 3) cellular factors that form protein-protein complexes with HIV-1 regulatory proteins; and 4) cellular genes which are modulated upon viral infection. With rapid increases in knowledge in the area of virus-cell interactions, we anticipate that this initial survey would be expanded extensively in future editions of the data base. Additional discussions on HIV-cell interactions are found elsewhere (Jones and Peterlin, 1994; Jeang and Gatignol, 1994; Garcia and Gaynor, 1994; Gatignol *et al*., 1996; Dayton, 1996).

I. DNA-binding Proteins

The promoter-enhancers of the human immunodeficiency virus (HIV) are contained in the U3 of the viral long terminal repeat (LTR). HIV-1 U3 is typically 454 nucleotides long and has binding sites for many transcription factors. Some of these are diagrammed in figure 1. With the exception of NF-kB and Sp1 (Ross *et al*., 1991; Kim *et al*., 1993; Huang and Jeang, 1993; Huang *et al*., 1994), verification of the importance of the various sequences in viral contexts has not been directly performed.

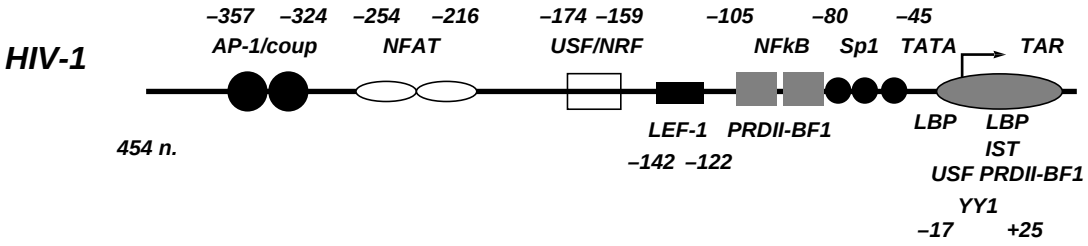

Fig. 1. Diagrammatic representation of the positions in U3 and R for some of the DNA-binding proteins that recognize the HIV-1 LTR.

Subgenomic assays in cultured cells indicate that the primary contributors to HIV-promoter activity are the NF-kB, Sp1, and TATAA (sequences from +1 to –105; Berkhout and Jeang, 1992). Nonetheless, it is likely that other DNA-binding factors also contribute *in vivo*. Beginning directionally from the 5′ end of U3, binding sites for AP-1 (a fos/jun hetero-complex; van Straaten *et al*., 1983; Hattori *et al*., 1988) and COUP (a member of the steroid/thyroid receptor superfamily; Cooney *et al*., 1991) are found between –324 to –357. Both COUP and AP-1 are expressed in human T-cells, and thus could compete with each other for the same proviral DNA sites during HIV-1 infection.

More proximally, between –216 and –254 are binding motifs for nuclear factor from activated T-cells (NFAT; Shaw *et al*., 1988). NFAT is an intermediating transducer of signals initiated at the T-cell antigen receptor. Recent evidence suggests that NFAT binding activity is composed of three discrete polypeptides, NFATp (McCaffrey *et al*., 1993), Fos and Jun (Yaseen *et al*., 1993).

In the region between –159 to –174 is a binding consensus sequence for USF (Gregor *et al*., 1990). USF was characterized initially as a positive activator of adenovirus major-late-promoter transcription. In the HIV context, there is conflicting information on whether this factor has moderating (and thus be regarded as a negative regulatory factor; NRF; Lu *et al*., 1990) or stimulating (Maekewa *et al*., 1991) effects. Interestingly, USF also binds a second unrelated sequence (–5 to +11) that surrounds the HIV-1 initiator (Hu *et al*., 1993). USF interaction at the initiator-proximal site activates strong expression from the TATAA-promoter (Hu *et al*., 1993). Of note, a factor distinct from USF, but which binds the same DNA-sequence, has also been cloned and characterized (TFE3; Bechmann and Kadesch, 1991).

LEF-1 is a T-cell specific transcription factor (Waterman and Jones, 1990). Once bound to its cognate site, LEF-1 bends DNA and thereby facilitates the assembly of nucleoprotein complexes at the promoter (Giese *et al*., 1992; reviewed in Jones and Peterlin, 1994). A high affinitiy LEF-1 binding site is present at –122 to –143. Two low affinity binding sites exist at –37 to –51 and +17 to +32 (Waterman and Jones, 1990).

NF-kB (Nabel and Baltimore, 1987) and Sp1 (Jones and Tjian, 1985; Jones *et al*., 1986) motifs are perhaps the best characterized sequence elements in the HIV-1 LTR. These sequences directly impact viral replication (Ross et al, 1991; Kim *et al*., 1993; Huang and Jeang, 1993; Huang *et al*., 1994), viral transcription (Harrich *et al*., 1990; Berkhout and Jeang, 1992; Pazin *et al*., 1996), and Tat transactivation (reviewed in Jones and Peterlin, 1994; Jeang and Gatignol, 1994). For more extensive discussions of the biochemical and functional properties of NF-kB (Ghosh *et al*., 1990; Kieran *et al*., 1990; Nolan *et al*., 1991; Liou *et al*., 1991; and references cited therein) and Sp1 (Dynan and Tjian, 1983; Briggs *et al*., 1986; Kadonaga *et al*., 1987; and references cited therein), readers should consult elsewhere.

PRDII-BF1 is a 300 kDa zinc-finger containing protein (Baldwin *et al*., 1990; Seeler *et al*., 1994). PRDII-BF1 recognizes and binds the NF-kB motif; however, it also binds a divergent sequence in R (+27 to +52; Seeler *et al*., 1994).

Positioned at the junction of U3 and R are sites for LBP (Yoon *et al*., 1994) and YY1 (Useheva and Shenk, 1994; Seto *et al*., 1991). While the role for LBP in HIV-1 transcription is not wholly understood (Jones *et al*., 1988; Kato *et al*., 1991), binding of YY1 to the LTR has been shown to repress HIV-1 expression and production of virions (Margolis *et al*., 1994). Besides LBP and YY1, a DNA-mediated activity for the induction of short transcripts (IST) has also been mapped to the same general vicinity (–5 to +26; Sheldon *et al*., 1993). The cDNA for the cellular factor that mediates IST-activity has not been isolated, and thus the authentic identity of this factor is unknown. HIP 116 is another newly cloned cDNA that binds to the TATA/initiator of the HIV-1 promoter (Sheridan *et al*., 1995).

There are a number of reports of sites for DNA-binding proteins in the HIV-1 genome that occur downstream of the +1 start for transcription. These include NF-kB motifs (Mallardo *et al*., 1996) and sites for AP-1, AP-3-like, DBF-1, and Sp-1 (El Kharroubi and Martin, 1996). The full implication of these downstream DNA-motifs in the setting of HIV-1 infection remains to be clarified.

II. RNA-binding Proteins

In recent years, it has become evident that RNA-binding proteins play important roles in gene regulation (see reviews, Keene and Query, 1991; Mattaj, 1993; Burd and Dreyfuss, 1994). For HIV-1, cellular proteins that bind viral regulatory RNAs have been studied in detail. In particular, at least eight host cell factors have been described to bind TAR RNA. Similarly, two RRE-binding factors have been characterized. There are also biologically compelling reasons as to why TAR- and RRE- binding proteins are meaningful contributors to the HIV-1 lifecycle.

The HIV-1 leader RNA, TAR, forms a stem-bulge-loop structure of approximately 60+ nucleotides (Muesing *et al*., 1987; Berkhout and Jeang, 1989). Early, it was reported that many human cellular proteins bound TAR RNA (Gatignol *et al*., 1989; Gaynor *et al*., 1989). Since then, some of these factors have been defined further. Tabulating from extant studies, eight proteins associate with either the bulge, loop, or stem of TAR RNA (see fig. 2). TAR loop-binding proteins include p68 (Marciniak *et al*., 1990), and TRP1/TRP185 (185 kDa; Sheline *et al*., 1991; Wu *et al*., 1991), while TRP2 (70–110 kDa; Sheline *et al*., 1991) binds to TAR-bulge. Proteins that complex with the double-stranded stem of TAR RNA

consist of P1/dsI (newly renamed as PKR; McCormack et al., 1992; Roy *et al*., 1991), SBP (140 kDa; Rounseville and Kumar, 1992), and TRBP (Gatignol *et al*., 1991; Gatignol *et al*., 1993). Two human autoantigens have been identified as TAR RNA-binding factors: Lupus antigen Ku (Kaczmarski and Khan, 1993) binds to the loop of TAR, while La (Chang *et al*., 1994; Svitkin *et al*., 1994) recognizes U-residues within the overall context of the TAR secondary structure.

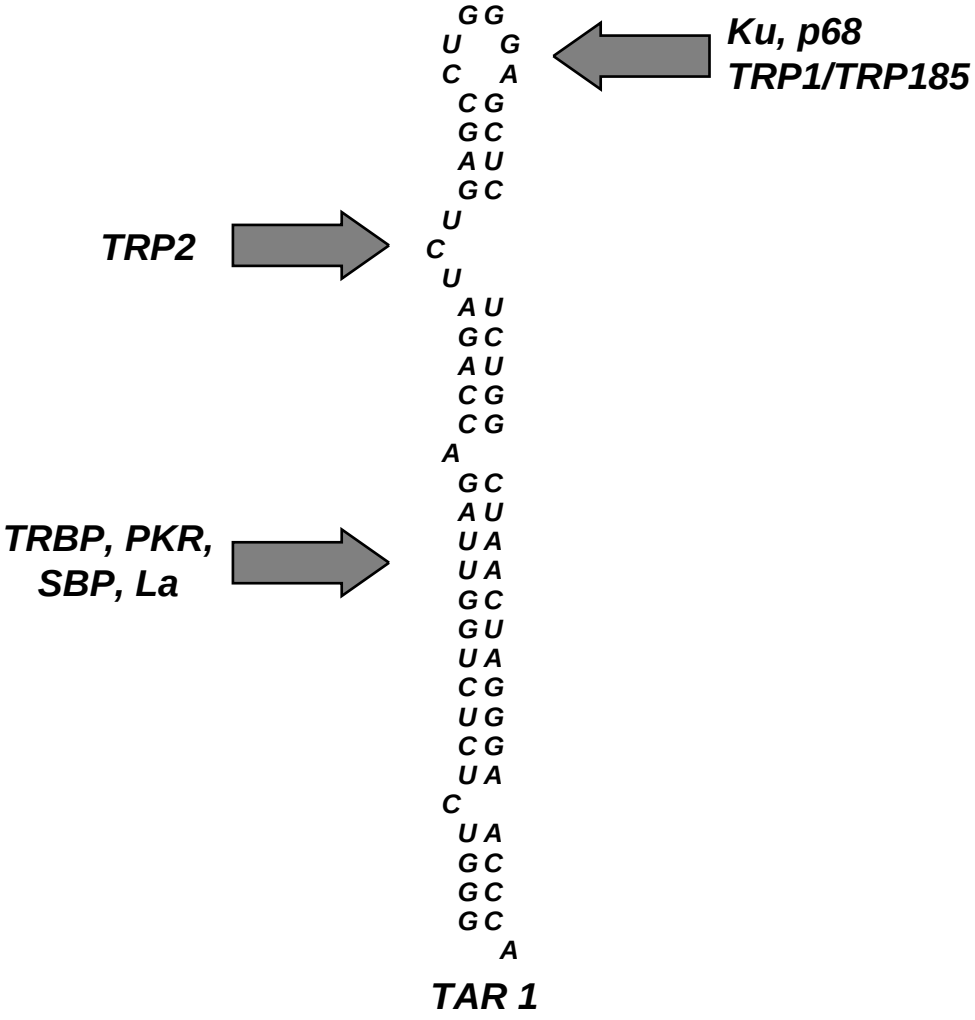

Fig. 2. Structure of the HIV-1 TAR RNA. Identities of the proteins that bind to the loop, bulge or stem of the TAR hairpin are indicated.

Recently, additional TAR-RNA-binding proteins and co-factors have been reported. Wong-Staal and colleagues have described the binding of TARBP-b (Reddy *et al*., 1995) to the bulge structure of TAR. A set of cellular co-factors that enhances the binding of TRP 185 and RNA polymerase II (RNAP II) to TAR have been described by Gaynor and colleagues (Wu-Baer *et al*., 1996a; 1996b). Finally, Hart and co-workers have characterized the elusive human chromosome 12-associated TAR loop-binding factor as an 83-kilodalton primate cell-specific protein whose expression is constitutively absent in hamster cells (Hart *et al*., 1995).

RRE-binding proteins have also been studied extensively. We know that TRBP also can bind RRE (Park *et al*., 1994). A 56 kDa factor (Vaishnav *et al*., 1992) and a 49 kDa protein that belongs to

the heterogeneous nuclear ribonuclear protein family (Xu *et al*., 1996) have been reported to bind RRE. Two other factors of 120 kDa and 60 kDa in molecular size have been reported to be primate-specific RRE-binding factors that are not expressed in rodent cells (Shukla *et al*., 1994). It is expected that other RRE-factors would emerge from future studies. How these, as yet poorly characterized, factors might contribute to Rev/RRE function is reviewed in detail elsewhere (Dayton, 1996).

III. Protein-protein interactions

Protein-protein interactions are well-documented to be important in gene regulation (see reviews, Lewin, 1990; Greenblatt, 1991). Recent studies suggest that many HIV-1 proteins complex with host cell factors. We briefly describe below some examples pertaining to Tat, Rev, Gag, and Nef.

Although Tat is best known for transcription, it has other functions (Huang *et al*., 1994; reviewed in Chang *et al*., 1995; Goldstein, 1996) and has been reported to be a secretable factor that promotes the growth of Kaposi-like cells (Ensoli *et al*., 1990). There is evidence that Tat can be taken up actively into cells (Frankel and Pabo, 1988) through binding to a cell-surface protein (Weeks *et al*., 1993) implicated to be $\alpha_v\beta_5$ integrin (Vogel *et al*., 1993). Once inside cells, Tat interacts with multiple partners in activating transcription (see also Tat Structure and Function section; Part III).

Two factors that bind Tat are themselves critical components of the eucaryotic RNA polymerase II transcription machinery. Genetic evidence supports a critical role for Sp1 in HIV-1 Tat-mediated transactivation (Harrich *et al*., 1989; Kamine *et al*., 1991; Southgate and Green, 1991; Berkhout and Jeang, 1992). Interestingly, direct protein-protein interactions between Tat and Sp1 (Jeang *et al*., 1993) and Tat and the thyroid hormone receptor (which in certain cells bind at the Sp1 sites in the HIV-1 LTR; Desai-Yajnik *et al*., 1995) have been documented. In addition, there is evidence that Tat also contacts TBP (Kashanchi *et al*., 1994) and that Tat-Sp1-TFIID could present as a multiprotein complex (Huang *et al*., 1993) inside cells. The critical nature of Tat-TBP contact has been questioned recently (Wang *et al*., 1996). These investigators found that a trans-activation defective Tat protein bound TBP with the same avidity as wild type Tat protein, suggesting that binding to TBP cannot solely reflect the trans-activation property of Tat.

A large family of proteins related to the 26S protease from human erythrocytes (Dubiel *et al*., 1994) are Tat-binding polypeptides. Members of this family include TBP-1 (Nelbock *et al*., 1990; Ohana *et al*., 1993), TBP-7 (Ohana *et al*., 1993; Shaw and Ennis, 1993), MSS1 (Shibuya *et al*., 1992), and SUG1 (Swaffield *et al*., 1992). The exact role of this family of proteins in cellular metabolism is not wholly clear; however, the 26S protease seems to regulate the degradation of some cyclins and in this manner has been implicated in modulating the stability of oncoproteins such as c-Mos, c-Myb, c-Myc and p53 (Dubiel *et al*., 1994).

Other cellular proteins, a 36 kDa protein (Desai *et al*., 1991), a 60 kDa protein (Kamine *et al*., 1996), and different cellular protein kinases (Hermann and Rice, 1993; McMillan *et al*., 1995; Zhou and Sharp, 1996; Chun and Jeang, 1996), have been reported to bind Tat. Mavankal and colleagues have suggested that RNA polymerase II (RNAP II) is itself a specific Tat-binding protein (Mavankal *et al*., 1996). The findings that RNAP II and kinases that phosphorylate RNAP II are Tat-binding factors suggest that these components contribute a part to explaining Tat function in transcription.

Multiple cellular factors also interact with Rev. Rev localizes to the nucleoli, and work by Laemmli and colleagues (Fankhauser *et al*., 1991) and others (Miyazaki *et al*. 1995; Szebeni *et al*., 1995) have demonstrated a tight association between the basic nuclear-localizing domain of Rev and nucleolar B23 protein. This protein-protein complex likely directs the subcellular localization of Rev.

By contrast, many investigators have studied the nuclear export function of Rev (Fischer *et al*., 1994; 1995; Wen *et al*., 1995; Myer *et al*., 1996; Fridell *et al*., 1996). Using the yeast two-hybrid cloning approach, three groups have isolated closely related nucleoporin proteins that bind wild type but not mutant Rev (Fritz *et al*., 1995; Bogerd et al., 1995; Stutz *et al*., 1995). These results suggest that the nucleoporin class of proteins are the Rev activation-domain specific co-factors involved in the nuclear to cytoplasmic export of RNAs.

Rev function can also be modulated by associations with other cellular factors. Two additional proteins have been shown to bind Rev. These are translation factor eIF-5A (Ruhl *et al*., 1993; Bevec *et al*., 1996), and serine-arginine (SR)-rich factors (Gontarek and Derse, 1996) such as the p32 protein (Luo *et al*., 1994; Tange *et al*., 1996) originally characterized by Krainer and colleagues (Krainer *et al*., 1991) as a splicing factor-SF2-associated polypeptide. SR-rich proteins can also bind to the basic domain of the HIV-1 and HIV-2 Tat proteins (Trinh and Jeang, unpublished observation; B.R. Cullen, personal communication).

Other less-characterized Rev-binding proteins include human prothymosin alpha (Kubota et al, 1995) and nuclear lamin B (Nikolakaki et al, 1996).

Both HIV Gag and Nef also have cellular partners. p55 and p24 Gag bind cyclophilin A and cyclophilin B proteins (Luban *et al*., 1993). The cyclophilins are cellular polypeptides originally characterized for their specific binding to cyclosporin A.

Nef has been found to bind β-COP, a coat protein from non-clathrin-coated vesicles (Benichou *et al*., 1994). This interaction may be important in promoting the intracellular sequestration of CD4. Nef has also been shown to interact directly with CD4 (Rossi *et al*., 1996). Recently many kinases have been described to associate with Nef (Sawai *et al*., 1994; Saksela *et al*., 1995; Bodeus *et al*., 1995; Luo and Garcia, 1996). The identity of some of these kinases include Lck (Salghetti *et al*., 1995; Collette *et al*., 1996), Hck (Lee *et al*., 1995), and PAK (Nunn and Marsh, 1996). Undoubtedly, there is much more to be learned from this area of research.

IV. Cellular Genes Modulated by HIV

Infection of cells by HIV results in activation and repression of many cellular genes. Because of the complexity of ambient gene expression inside cells, it is logistically difficult to dissect those genes that are upregulated from those that are downregulated from others that remain unperturbed. Nevertheless, several examples of genes that respond to HIV infection are known. Some of these include IL-2 (Westendorf *et al*., 1994), IL6 (Scala *et al*., 1994), and TGF-β (Buonaguro *et al*., 1994; Rasty *et al*., 1996).

Recent investigations have shown that HIV-1 proteins such as Tat and Nef potently affect cellular metabolism. Tat, for example, has been shown to modulate the expression of cytokines including MIP-1 alpha (Sharma *et al*., 1996), second messengers including nitric oxide (Barton *et al*., 1996), and housekeeping genes such as Bcl2 (Zauli *et al*., 1995a). Both Tat and Nef participate in signal transduction pathways that include NF-kB (Demarchi *et al*., 1996), phosphatidylinositol kinase (Zauli et al; 1995b; Gramagli et al., 1996), and protein kinase C (Conant *et al*., 1996)

The identification of genes modulated by HIV has been based on classical approaches; however, with the advent of mRNA differential display technology (Liang and Pardee, 1992) the exhaustive characterization of cellular genes that respond to infection by HIV should be accomplished with greater ease. One such example has recently been reported. Zeichner and colleagues, using a differential display approach, found that expression of the human glucose transporter protein (GLUT3) is upregulated by HIV-1 infection. We anticipate reports on others, shortly.

References

[1] Baldwin, A. S. J., K. P. LeClair, H. Singh, and P. A. Sharp. 1990. A large protein containing zinc finger domains binds to related sequence elements in the enhancers of the class I major histocompatibility complex and kappa immunoglobulin genes. *Mol. Cell. Biol.* **10**:1406–1414.

[2] Barton, C. H., T. E. Biggs, T. R. Mee, and D. A. Mann. 1996. The human immunodeficiency virus type 1 regulatory protein Tat inhibits interferon-induced iNos activity in a murine macrophage cell line. *J. Gen. Virol.* **77**(Aug Pt 8):1643–1647.

[3] Beckmann, H., and T. Kadesch. 1991. The leucine zipper of TEF3 dictates helix-loop-helix dimerization specificity. *Genes Dev.* **5**:1057–1066.

[4] Benichou, S., M. Bomsel, M. Bodeus, H. Durand, M. Doute, F. Letourneur, J. Camonis, and R. Benarous. 1994. HIV-1 nef interacts with B-COP, a coat protein from non-clathrin-coated vesicles. *J. Biol. Chem*. **269**: 30073–30076.

[5] Berkhout, B., and K.-T. Jeang. 1989. trans Activation of human immunodeficiency virus type 1 is sequence specific for both the single-stranded bulge and loop of the trans-acting-responsive hairpin: a quantitative analysis. *J. Virol*. **63**:5501–5504.

[6] Berkhout, B., and K.-T. Jeang. 1992. Functional roles for the TATA promoter and enhancers in basal and Tat-induced expression of the Human Immunodeficiency virus type 1 long terminal repeat. *J. Virol*. **66**:139–149.

[7] Berkhout, B., R. H. Silverman, and K.-T. Jeang. 1989. Tat trans-activates the human immunodeficiency virus through a nascent RNA target. *Cell* **59**:273–282.

[8] Bevec, D., H. Jaksche, M. Oft, T. Wohl, M. Himmelspach, A. Pacher, M. Schebesta, K. Koettnitz, M. Dobrovnik, R. Csonga, F. Lottspeich, and J. Hauber. 1996. Inhibition of HIV-1 replication in lymphocytes by mutants of the Rev cofactor eIF-5A. *Science* **271**:1858–1860.

[9] Bodeus, M., A. Marie-Cardine, C. Bougeret, F. Ramos-Morales, and R. Benarous. 1995. *In vitro* binding and phosphorylation of human immunodeficiency virus type 1 Nef protein by serine/threonine protein kinase. *J. Gen. Virol*. **76**:1337–1344.

[10] Bogerd, H. P., R. A. Fridell, S. Madore, and B. R. Cullen. 1995. Identification of a novel cellular cofactor for the Rev/Rex class of retroviral regulatory proteins. *Cell* **82**:485–494.

[11] Braddock, M., R. Powell, A. D. Blanchard, A. J. Kingsman, and S. M. Kingsman. 1993. HIV-1 TAR RNA-binding proteins control TAT activation of translation in Xenopus oocytes. *FASEB J*. **7**:214–222.

[12] Briggs, M. R., J. T. Kadonaga, S. P. Bell, and R. Tjian. 1986. Purification and biochemical characterization of the promoter specific transcription factor, Sp1. *Science* **234**:47–52.

[13] Buonaguro, L., F. M. Buonaguro, G. Giraldo, and B. Ensoli. 1994. The human immunodeficiency virus type 1 Tat protein transactivates tumor necrosis factor beta gene expression through a TAR-like structure. *J. Virol*. **68**:2677–2682.

[14] Burd, C. G., and G. Dreyfuss. 1994. Conserved structures and diversity of functions of RNA-binding proteins. *Science* **265**:615–621.

[15] Chang, H. K., R. C. Gallo, and B. Ensoli. 1995. Regulation of cellular gene expression and function by the human immunodeficiency virus type 1 Tat protein. *J. Biomed. Sci* **2**:189–202.

[16] Chang, Y., D. J. Kenan, J. Keene, A. Gatignol, and K. T. Jeang. 1994. Direct interactions between the autoantigen La and the human immunodeficiency virus (HIV-1) leader RNA. *J. Virol*. **68**:7008–7020.

[17] Chun, R., and K.-T. Jeang. 1996. Requirements for RNA polymeraseII carboxyl-terminal domain for activated transcription of human retroviruses human T-cell lymphotropic virus I and HIV-1. *J. Biol. Chem*. **271**:27888–27894.

[18] Collette, Y., H. Dutartre, A. Benziane, A. Romas-Morales, R. Benarous, M. Harris, and D. Olive. 1996. Physical and functional interaction of Nef with Lck. HIV-1 Nef-induced T-cell signaling defects. *J. Biol. Chem*. **271**:6333–6341.

[19] Conant, K., M. Ma, A. Nath, and E. O. Major. 1996. Extracellular human immunodeficiency virus type 1 Tat protein is associated with an increase in both NF-kappa B binding and protein kinase C activity in primary human astrocytes. *J. Virol*. **70**:1384–1389.

[20] Cooney, A. J., S. Y. Tsai, B. W. O'Malley, and M.-J. Tsai. 1991. Chicken ovalbumin upstream promoter transcription factor binds to a negative regulatory region in the human immunodeficiency virus type 1 long terminal repeat. *J. Virol*. **65**:2853–2860.

[21] Dayton, A. I. 1996. The Rev axis and its associated host cofactors: a viral window onto the workings of eukaryotic posttranscriptional RNA processing. *Journal of Biomedical Science* **3**:69–77.

[22] Demarchi, F., di F. F. d'Adda, A. Falaschi, and M. Giacca. 1996. Activation of transcription factor NF-kappaB by the Tat protein of human immunodeficiency virus type 1. *J. Virol*. **70**:4427–4437.

[23] Desai, K., P. M. Lowenstein, and M. Green. 1991. Isolation of a cellular protein that binds to the human immunodificiency virus Tat protein and can potentiate transactivation of the viral promoter. *Proc. Natl. Acad. Sci. USA* **88**:8875–8879.

[24] Desai-Yajnik, V., E. Hadzic, P. Modlinger, S. Malhotra, G. Gechlik, and H. H. Samuels. 1995. Interactions of thyroid hormone receptor with the human immunodeficiency virus type 1 (HIV-1) long terminal repeat and the HIV-1 Tat transactivator. *J. Virol*. **69**:5103–5112.

[25] Du, H., A. L. Roy, and R. G. Roeder. 1993. Human transcription factor USF stimulates transcription through the initiator elements of the HIV-1 and the Ad-ML promoters. *EMBO J*. **12**:501–511.

[26] Dubiel, W., K. Ferrell, and M. Rechsteiner. 1994. Tat-binding protein 7 is a subunit of the 26S protease. *Biol. Chem. Hoppe-Seyler* **375**:237–240.

[27] Dynan, W. S., and R. Tjian. 1983. Isolation of transcriptionfactors that discriminate between different promoters recognized by RNA polymerase II. *Cell* **32**:669–680.

[28] El Kharroubi, A., and M. A. Martin. 1996. cis-Acting sequences located downstream of the human immunodeficiency virus type 1 promoter affect its chromatin structure and transcriptional activity. *Mol. Cell. Biol*. **16**:2958–2966.

[29] Ensoli, B., G. Barillari, S. Z. Salahuddin, R. C. Gallo, and F. Wong-Staal. 1990. Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. *Nature* **345**:84–86.

[30] Fankhauser, C., E. Izaurralde, Y. Adachi, P. Wingfield, and U. K. Laemmli. 1991. Specific complex of human immunodeficiency virus type 1 Rev and nucleolar B23 proteins: dissociation by the Rev response element. *Mol. Cell. Biol*. **11**:2567–2575.

[31] Fischer, U., J. Huber, W. C. Boelens, I. W. Mattaj, and R. Luhrmann. 1995. The HIV-1 Rev activation domain is a nuclear export signal that accesses an export pathway used by specific cellular RNAs. *Cell* **82**:475–483.

[32] Fischer, U., S. Meyer, M. Teufel, C. Heckel, R. Luhrmann, and G. Rautmann. Evidence that HIV-1 Rev directly promotes the nuclear export of unspliced RNA. *EMBO J*. **13**:4105–4112.

[33] Frankel, A., and C. Pabo. 1988. Cellular uptake of the Tat protein from human immunodeficiency virus. *Cell* **55**:1189–1193.

[34] Fridell, R. A., H. P. Bogerd, and B. R. Cullen. 1996. Nuclear export of late HIV-1 mRNAs occurs via a cellular protein export pathway. *Proc. Natl. Acad. Sci. USA* **93**:4421–4424.

[35] Fritz, C. C., M. L. Zapp, and M. R. Green. 1995. A human nucleoporin-like protein that specifically interacts with HIV Rev. *Nature* **376**:530–533.

[36] Garcia, J. A., and R. B. Gaynor. 1994. Regulatory mechanism involved in the control of HIV-1 gene expression. *J. AIDS* 8:S3–S17.

[37] Garcia, J. A., D. Harrich, E. Soultanakis, F. Wu, R. Mitsuyasu, and R. B. Gaynor. 1989. Human immunodeficiency virus type 1 LTR TATA and TAR region sequences required for transcriptional regulation. *EMBO J*. **8**:765–778.

[38] Garcia, J. A., F. K. Wu, R. Mitsuyasu, and R. B. Gaynor. 1987. Interactions of cellular proteins involved in the transcriptional regulation of the human immunodeficiency virus. *EMBO J*. **6**:3761–3770.

[39] Gatignol, A., C. Buckler, and K.-T. Jeang. 1993. Relatedness of an RNA binding motif in HIV-1 TAR RNA-binding protein TRBP to human P1/dsI kinase and Drosophila staufen. *Mol. Cell. Biol*. **13**:2193–2202.

[40] Gatignol, A., A. Buckler-White, B. Berkhout, and K.-T. Jeang. 1991. Characterization of a human TAR RNA-binding protein that activates the HIV-1 LTR. *Science* **251**:1597–1600.

[41] Gatignol, A., M. Duarte, L. Daviet, Y. N. Chang, and K. T. Jeang. 1996. Sequential steps in Tat trans-activation of HIV-1 mediated through cellular DNA, RNA, and protein binding factors. *Gene Exp*. **5**:217–228.

[42] Gatignol, A., A. Kumar, A. Rabson, and K.-T. Jeang. 1989. Identification of cellular proteins that bind to the human immunodeficiency virus type 1 trans-activation-responsive TAR element RNA. *Proc. Natl. Acad. Sci. USA* **86**:7828–7832.

[43] Gaynor, R., E. Soultanakis, M. Kuwabara, J. Garcia, and D. S. Sigman. 1989. Specific binding of a HeLa cell nuclear protein to RNA sequences in the human immunodeficiency virus transactivating region. *Proc. Natl. Acad. Sci. USA* **86**:4858–4862.

[44] Ghosh, S., A. M. Gifford, L. R. Fiviere, P. Tempst, G. P. Nolan, and D. Baltimore. 1990. Cloning of the p50 DNAbinding subunit of NF-kB: homology to rel and dorsal. *Cell* **62**:1019–1029.

[45] Giese, K., J. Cox, and R. Gosschedl. 1992. The HMG domain of lymphoid enhancer factor 1 bends DNA and facilitates assembly of functional nucleoprotein structures. *Cell* **69**:185–195.

[46] Goldstein, G. 1996. HIV-1 Tat protein as a potential AIDS vaccine. *Nat. Med*. **1**:960–964.

[47] Gontarek, R. R., and D. Derse. 1996. Interactions among SR proteins, an exonic splicing enhancer, and a lentivirus Rev protein regulate alternative splicing. *Mol. Cell. Biol*. **16**:2325–2331.

[48] Goyer, C., H. S. Lee, D. Malo, and N. Sonenberg. 1992. Isolation of a yeast gene encoding a protein homologous to the human Tat-binding protein, TBP-1. *DNA Cell Biol*. **13**:579–585.

[49] Graziani, A., F. Galimi, E. Medico, E. Cottone, D. Gramaglia, C. Boccaccio, and P. M. Comoglio. 1996. The HIV-1 nef protein interferes with phosphatidylinositol 3-kinase activation 1. *J. Biol. Chem*. **271**:6590–6593.

[50] Greenblatt, J. 1991. Roles of TFIID in transcriptional initiation by RNA polymerase II. *Cell* **66**:1067–1070.

[51] Gregor, P. D., M. Sawadago, and R. G. Roeder. 1990. The adenovirus major late transcription factor USF is a member of the helix-loop-helix group of regulatory proteins and binds to DNA as a dimer. *Genes Dev*. **4**:1730–1740.

[52] Han, X. M., A. Laras, M. P. Rouseville, A. Kumar, and P. R. Shank. 1992. Human immunodeficiency virus type 1 Tat-mediated trans activation correlates with the phosphorylation state of a cellular TAR RNA stem-binding factor. *J. Virol*. **66**:4065–4072.

[53] Harrich, D., J. Garcia, F. Wu, R. Mitsuyasu, J. Gonzalez, and R. B. Gaynor. 1989. Role of Sp1-binding domains in *in vivo* transcriptional regulation of the human immunodeficiency virus type 1 long terminal repeat. *J. Virol*. **63**:2585–2591.

[54] Hart, C. E., M. J. Saltrelli, J. C. Galphin, and G. Schochetman. 1995. A human chromosome 12-associated 83-kilodalton cellular protein specifically binds to the loop region of human immunodeficiency virus type 1 trans-activation response element RNA. *J. Virol*. **69**:6593–6599.

[55] Hattori, K., P. Angel, M. LeBeau, and M. Karin. 1988. Structure and chromosomal localization of the functional intronless human JUN protooncogene. *Proc. Natl. Acad. Sci. USA* **85**:9148–9152.

[56] Hermann, C. H., and A. P. Rice. 1993. Specific interaction of the human immunodeficiency virus Tat protein with a cellular protein kinase. *Virology* **197**:601–608.

[57] Huang, L. M., and K.-T. Jeang. 1993. Increased spacing between Sp1 and TATAA renders HIV-1 replication defective: Implication for Tat function. *J. Virol*. **67**:6937–6944.

[58] Huang, L. M., A. Joshi, R. Willey, J. Orenstein, and K. T. Jeang. 1994. Human immunodeficiency viruses regulated by alternative trans-activators: genetic evidence for a novel non-transcriptional function of Tat in virion infectivity. *EMBO J*. **13**:2886–2896.

[59] Jeang, K. T., R. Chun, N. H. Lin, A. Gatignol, C. G. Glabe, and H. Fan. 1993. In vitro and *in vivo* binding of human immunodeficiency virus type 1 Tat protein and Sp1 transcription factor. *J. Virol*. **67**:6224–6233.

[60] Jones, K. A., J. T. Kadonaga, P. A. Luciw, and R. Tjian. 1986. Activation of the AIDS retrovirus promoter by the cellular transcriptin factor, Sp1. *Science* **232**:755–759.

[61] Jones, K., P. Luciw, and N. Duchange. 1988. Structural arrangements of transcription control domains within the 5′ untranslated leader regions of HIV-1 and HIV-2 promoters. *Genes Dev*. **2**:1101–1114.

[62] Jones, K. A., and B. M. Peterlin. 1994. Control of RNA initiation and elongation at the HIV-1 promoter. *Annu. Rev. Biochem.* **63**:717–743.

[63] Jones, K. A., and R. Tjian. 1985. Sp1 binds to promoter sequences and activates herpes simplex virus "immediate-early" gene transcription *in vitro*. *Nature* **317**:179–182.

[64] Kaczmarski, W., and S. A. Khan. 1993. Lupus autoantigen Ku protein binds HIV-1 TAR RNA *in vitro*. *Biochem. Biophys. Res. Communications* **196**:935–942.

[65] Kadonaga, J. T., K. R. Carner, F. R. Masiarz, and R. Tjian. 1987. Isolation of cDNA encoding transcription factor Sp1 and functional analysis of the DNA binding domain. *Cell* **51**:1079–1090.

[66] Kamine, J., B. Elangovan, T. Subramanian, D. Coleman, and G. Chinnadurai. 1996. Identification of a cellular protein that specifically interacts with the essential cysteine region of the HIV-1 Tat transactivator. *Virology* **216**:357–366.

[67] Kamine, J., T. Subramanian, and G. Chinnadurai. 1991. Sp1-dependent activation of a synthetic promoter by human immunodeficiency virus type I Tat protein. *Proc. Natl. Acad. Sci. USA* **88**:8510–8514.

[68] Kashanchi, F., G. Piras, M. F. Radonovich, J. F. Duvall, A. Fattaey, C.-M. Chiang, R. G. Roeder, and J. N. Brady. 1994. Direct interaction of human TFIID with the HIV-1 transactivator Tat. *Nature* **367**:295–299.

[69] Kato, H., M. Horikoshi, and R. G. Roeder. 1991. Repression of HIV-1 transcription by a cellular protein. *Science* **251**:1476–1479.

[70] Kenan, D. J., C. C. Query, and J. D. Keene. 1991. RNA recognition: towards identifying determinants of specificity. *Trends Biochem. Sci.* **16**:214–220.

[71] Kieran, M., V. Blank, F. Logeat, J. Vandekerckhove, F. Lottspeich, O. LeBail, M. B. Urban, P. Kourilsky, P. A. Baeuerle, and A. Israel. 1990. The DNA binding subunit of NF-kB is identical to factor KBF-1 and homologous to the rel oncogene product. *Cell* **44**:261–272.

[72] Kim, J., F. Gonzalez-Scarano, S. Zeichner, and J. Alwine. 1993. Replication of type 1 human immunodeficiency viruses containing linker substitution mutations in the –201 to –130 region of the long terminal repeat. *J. Virol.* **67**:1658–1662.

[73] Krainer, A. R., A. Mayeda, D. Kozak, and G. Binns. 1991. Functional expression of cloned human splicing factor SF2: Homology to RNA-binding proteins, U1, 70k, and Drosophila splicing factor. *Cell* **66**:383–394.

[74] Kubota, S., Y. Adachi, T. D. Copeland, and S. Oroszlan. 1995. Binding of human prothymosin alpha to the leucine-motif/activation domains of HTLV-I Rex and HIV-1 Rev. *Eur. J. Biochem* **233**:48–54.

[75] Lee, C. H., B. Leung, M. A. Lemmon, J. Zheng, D. Cowburn, J. Kuriyan, and K. Saksela. 1995. A single amino acid in the SH3 domain of Hck determines its high affinity and specificity in binding to HIV-1 Nef protein. *EMBO J.* **14**:5006–5015.

[76] Lee, J.-S., K. M. Galvin, and Y. Shi. 1993. Evidence for physical interaction between the zinc-finger transcription factor YY1 and Sp1. *Proc. Natl. Acad. Sci. USA* **90**:6145–6149.

[77] Lewin, B. 1990. Commitment and activation at PolII promoters: a tail of protein-protein interactions. *Cell* **61**:1161–1164.

[78] Li, C., C. Lai, D. S. Sigman, and R. Gaynor. 1991. Cloning of a cellular factor, interleukin binding factor, that binds to NFAT-like motifs in the human immunodeficiency virus long terminal repeat. *Proc. Natl. Acad. Sci. USA* **88**:7739–7743.

[79] Liang, P., and A. B. Pardee. 1992. Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction. *Science* **257**:967–971.

[80] Liou, H. C., G. P. Nolan, S. Ghosh, F. Fujita, and D. Baltimore. 1992. The NF-kB p50 precursor, p105 contains an internal IkB-like inhibitor that preferentially inhibits p50. *EMBO J.* **11**:3003–3009.

[81] Lu, Y., N. Touzjian, M. Stenzel, T. Dorfman, J. G. Sodroski, and W. A. Haseltine. 1990. Identification of cis-acting repressive sequences within the negative regulatory element of human immunodeficiency virus type 1. *J. Virol.* **64**:5226–5229.

[82] Luban, J., K. L. Bossolt, E. K. Franke, K. V. Ganjam, and S. P. Goff. 1993. Human immunodeficiency virus type 1 gag protein binds to cyclophilins A and B. *Cell* **73**:1067–1078.

[83] Luo, T., and J. V. Garcia. 1996. The association of Nef with a cellular serine/threonine kinase and its enhancement of infectivity are viral isolate dependent. *J. Virol*. **70**:6493–6496.

[84] Luo, Y., H. Yu, and B. M. Peterlin. 1994. Cellular protein modulates effects of human immunodeficiency virus type 1 Rev. *J. Virol*. **68**:3850–3856.

[85] Maekewa, T., T. Sudo, M. Kurimote, and S. Ishii. 1991. USF-related transcription factor, HIV-TF1, stimulates transcription of human immunodeficiency virus-1. *Nucl. Acids. Res*. **19**:4689–4694.

[86] Mallardo, M., E. Dragonetti, F. Baldassarre, C. Ambrosino, G. Scala, and I. Quinto. 1996. An NF-kB site in the 5′-untranslated leader regiion of the human immunodeficiency virus type 1 enhances the viral expression in response to NF-kB-activating stimuli. *J. Biol. Chem*. **271**:20820–20827.

[87] Marciniak, R. A., M. A. Garcia-Blanco, and P. A. Sharp. 1990. Identification and characterization of a HeLa nuclear protein that specifically binds to the trans-activation-response (TAR) element of human immunodeficiency virus. *Proc. Natl. Acad. Sci. USA* **87**:3642–3646.

[88] Margolis, D. M., M. Somasundaran, and M. R. Green. 1994. Human transcription factor YY1 represses human immunodeficiency virus type 1 transcription and virion production. *J. Virol*. **68**:905–910.

[89] Mattaj, I. W. 1993. RNA recognition: A family matter? *Cell* **73**:837–840.

[90] Mavankal, G., O. S. H. Ignatius, H. Oliver, D. Sigman, and R. B. Gaynor. 1996. Human immunodeficiency virus type 1 and 2 Tat proteins specifically interact with RNA polymerase II. *Proc. Natl. Acad. Sci. USA* **93**:2089–2094.

[91] McCaffrey, P., C. Luo, T. Kerppola, J. Jain, T. Badalian, A. Ho Burgeon, E., W. Lane, J. Lambert, T. Curran, G. Verdine, A. Rao, and P. G. Hogan. 1993. Isoation of the cyclosporin-sensitive T cell transcription factor NFATp. *Science* **262**:750–754.

[92] McCormack, S., D. Thomis, and C. Samuel. 1992. Mechanism of interferon action: identification of a RNA-binding domain within the N-terminal region of the human RNA dependent P1/eIF-2 alpha protein kinase. *Virology* **188**:47–56.

[93] McMillan, N. A., R. F. Chun, D. P. Siderovski, J. Galabru, W. M. Toone, C. E. Samuel, T. W. Mak, A. G. Hovanessian, K. T. Jeang, and B. R. Williams. 1995. HIV-1 Tat directly interacts with the interferon-induced, double-stranded RNA-dependent kinase, PKR. *Virology* **213**:413–424.

[94] Meyer, B. E., J. L. Meinkoth, and M. H. Malim. 1996. Nuclear transport of human immunodeficiency virus type 1, visna virus, and equine infectious anemia virus Rev proteins: identification of a family of transferable nuclear export signals. *J. Virol*. **70**:2350–2359.

[95] Miyazaki, Y., T. Takamatsu, T. Nosaka, S. Fujita, T. E. Martin, and M. Hatanaka. 1995. The cytotoxicity of human immunodeficiency virus type 1 Rev: implications for its interaction with the nucleolar protein B23. *Exp. Cell. Res*. **219**:93–101.

[96] Muesing, M., D. Smith, and D. Capon. 1987. Regulation of mRNA accumulation by human immunodeficiency virus trans-activator protein. *Cell* **48**:691–701.

[97] Nabel, G., and D. Baltimore. 1987. An inducible transcription factor activates expression of human immunodeficiency virus in T cells. *Nature* **326**:711–713.

[98] Nelbrock, P., P. Dillon, A. Perkins, and C. A. Rosen. 1990. A cDNA for a protein that interacts with the human immunodeficiency virus Tat transactivator. *Science* **248**:1650–1653.

[99] Nikolakaki, E., G. Simos, S. D. Georgatos, and T. Giannakouros. 1996. A nuclear envelope-associated kinase phosphorylates arginine-serine motifs and modulates interactions between the lamin B receptor and other nuclear proteins. *J. Biol. Chem*. **271**:8365–8372.

[100] Nolan, G., S. Ghosh, H. C. Liou, P. Tempst, and D. Baltimore. 1991. DNA-binding and IkB inhibition of the cloned p65 subunit of NF-kB, a rel-related polypeptide. *Cell* **64**:961–969.

[101] Nunn, M. F., and J. W. Marsh. 1996. Human immunodeficiency virus type 1 Nef associates with a member of the p21-activated kinase family. *J. Virol*. **70**:6157–6161.

[102] Ohana, B., P. A. Moore, S. M. Ruben, C. D. Southgate, M. R. Green, and C. A. Rosen. 1993. The type1 human immunodeficiency virus Tat binding protein is a transcriptional activator belonging to an additional family of evolutionarily conserved genes. *Proc. Natl. Acad. Sci. USA* **90**:138–142.

[103] Park, H., M. V. Davis, J. O. Langland, H. Chang, Y. Nam, J. Tartaglia, E. Paoletti, B. L. Jacobs, R. Kaufman, and S. Venkatesan. 1994. TAR RNA-binding protein is an inhibitor of the interferon-induced protein kinase PKR. *Proc. Natl. Acad. Sci. USA* **91**:4713–4717.

[104] Pazin, M. J., P. L. Sheridan, K. Cannon, Z. Cao, J. G. Keck, J. T. Kadonaga, and K. A. Jones. 1996. NF-kappa B-mediated chromatin reconfiguration and transcriptional activation of the HIV-1 enhancer *in vitro*. *Genes Dev*. **10**:37–49.

[105] Pengue, G., A. Caputo, C. Rossi, G. Barbanti-Brodano, and L. Lania. 1995. Transcriptional silencing of human immunodeficiency virus type 1 long terminal repeat-driven gene expression by the Kruppel-associated box repressor domain targeted to the transactivating response element. *J. Virol*. **69**:6577–6580.

[106] Pfeifer, K., B. Weiler, D. Ugarkovic, M. Bachmann, H. C. Schroder, and W. E. G. Muller. 1991. Evidence for a direct interaction of Rev protein with nuclear envelope mRNA-translocation system. *Eur. J. Biochem* **199**:53–64.

[107] Rasty, S., P. Thatikunta, J. Gordon, K. Khalili, S. Amini, and J. C. Glorioso. 1996. Human immunodeficiency virus tat gene transfer to the murine central nervous system using a replication-defective herpes simplex virus vector stimulates transforming growth factor beta 1 gene expression. *Proc. Natl. Acad. Sci. USA* **93**:6073–6078.

[108] Reddy, T. R., M. Suhasini, J. Rappaport, D. J. Looney, G. Kraus, and F. Wong-Staal. 1995. Molecular cloning and characterization of a TAR-binding nuclear factor from T cells. *AIDS. Res. Hum. Retroviruses* **11**:663–669.

[109] Ross, E., A. Buckler-White, A. B. Rabson, G. Englund, and M. A. Martin. 1991. Contribution of NF-kB and Sp1 binding motifs to the replicative capacity of human immunodeficiency virus type 1: distinct patterns of viral growth are determined by T-cell types. *J. Virol*. **65**:4350–4358.

[110] Rossi, F., A. Gallina, and G. Milanesi. 1996. Nef-CD4 physical interaction sensed with the yeast two-hybrid system. *Virology* **217**:397–403.

[111] Rounseville, M. P., and A. Kumar. 1992. Binding of a host cell nuclear protein to the stem region of human immunodeficiency virus type 1 trans-activation-responsive RNA. *J. Virol*. **66**:1688–1694.

[112] Roy, S., M. Agy, A. Horvenessian, N. Sonenberg, and M. Katze. 1991. The integrity of the stem structure of human immunodeficiency virus type 1 Tat-responsive sequence RNA is required for interaction witht he interferon-induced 68,000–Mr protein kinase. *J. Virol*. **65**:632–640.

[113] Ruhl, M., M. Himmelspach, G. M. Bahr, F. Hammerschmid, H. Jaksche, B. Wolff, H. Aschauer, G. K. Farrington, H. Probst, D. Bevec, *et al*. 1993. Eukaryotic initiation factor 5A is a cellular target of the human immunodeficiency virus type 1 Rev activation domain mediating trans-activation. *J. Cell Biol*. 123(6 Pt 1):1309–1320.

[114] Ruhl, M., M. Himmelspach, G. M. Bahu, F. Mammerschmid, B. Jaksche, H. Wolffe, H. Aschauer, G. K. Farrington, H. Probst, D. Bevec, and J. Hauber. 1993. Eukaryotic initiation factor 5A is a acellular target of the human immunodeficiency virus type 1 rev activation domain mediating trans-activation. *J. Cell Biol*. **123**:1309–1320.

[115] Saksela, K., G. Cheng, and D. Baltimore. 1995. Proline-rich (PxxP) motifs in HIV-1 Nef bind to SH3 domains of a subset of Src kinases and are required for the enhanced growth of Nef+ viruses but not for down-regulation of CD4. *EMBO J*. **14**:484–491.

[116] Salghetti, S., R. Mariani, and J. Skowronski. 1995. Human immunodeficiency virus type 1 Nef and p56lck protein-tyrosine kinase interact with a common element in CD4 cytoplasmic tail. *Proc. Natl. Acad. Sci. USA* **92**:349–353.

[117] Sawai, E. T., A. Baur, H. Struble, B. M. Peterlin, J. A. Levy, and C. Cheng-Mayer. 1994. Human immunodeficiency virus type 1 Nef associates with a cellular serine kinase in T lymphocytes. *Proc. Natl. Acad. Sci. USA* **91**:1539–1543.

[118] Scala, G., M. R. Ruocco, C. Ambrosino, M. Mallardo, V. Giordano Baldassarre, F., E. Dragonetti, I. Quinto, and S. Venuta. 1994. The expression of the interleukin 6 gene is induced by the human immunodeficiency virus 1 tat protein. *J. Exp. Med*. **179**:961–971.

[119] Seeler, J. S., C. Muchardt, A. Suessle, and R. Gaynor. 1994. Transcription factor PRDII-BF1 activates human immunodeficiency virus type 1 gene expression. *J. Virol*. **68**:1002–1009.

[120] Seto, E., Y. Shi, and T. Shenk. 1991. YY1 is an initiator sequence-binding protein that directs and activates transcription *in vitro*. *Nature* **354**:241–245.

[121] Sharma, V., M. Xu, L. M. Ritter, and N. M. Wilkie. 1996. HIV-1 tat induces the expression of a new hematopoietic cell-specific transcription factor and downregulates MIP-1 alpha gene expression in activated T-cells. *Biochem. Biophys. Res. Commun*. **223**:526–533.

[122] Shaw, D., and H. L. Ennis. 1993. Molecular cloning and developmental regulation of dictyostelium discoiceum homologues of the human and yeast HIV1 tat-binding protein. *Biochem. Biophys. Res. Commun*. **193**:1291–1296.

[123] Shaw, J., P. Utz, D. Durand, J. Tooole, E. Emmel, and G. R. Crabtree. 1988. Identification of a putative regulator of early T cell activation genes. *Science* **244**:202–205.

[124] Sheldon, M., R. Ratnasabapathy, and N. Hernandez. 1993. Characterization of the inducer of short transcripts, a human immunodeficiency virus type 1 transcriptional element that activates the synthesis of short transcripts. *Mol. Cell. Biol*. **13**:1251–1263.

[125] Sheline, C. T., L. H. Milocco, and K. A. Jones. 1991. Two distinct nuclear transcription factors recognize loop and bulge residues of the HIV-1 TAR RNA hairpin. *Genes Dev*. **5**:2508–2520.

[126] Sheridan, P. L., M. Schorpp, M. L. Voz, and K. A. Jones. 1995. Cloning of an SNF2/SWI2-related protein that binds specifically to the SPH motifs of the SV40 enhancer and to the HIV-1 promoter. *J. Biol. Chem*. **270**:4575–4587.

[127] Shibuya, H., K. Irie, J. Ninomiya-Tsuji, M. Goebl, T. Taniguchi, and K. Matsumot. 1992. New human gene encoding a positive modulator of HIV Tat-mediated transactivation. *Nature* **357**:700–702.

[128] Shukla, R. R., P. L. Kimmel, and A. Kumar. 1994. Human immunodeficiency virus type 1 Rev-responsive element RNA binds to host cell-specific proteins. *J. Virol*. **68**:2224–2229.

[129] Sorbara, L. R., F. Maldarelli, G. Chamoun, B. Schiulling, S. Chokekijcahi, L. Staudt, H. Mitsuya, I. A. Simpson, and S. L. Zeichner. 1996. Human immunodficiency virus type 1 infection of H9 cells induces increased glucose transporter expression. *J. Virol*. **70**:7275–7279.

[130] Stutz, F., M. Neville, and M. Rosbash. 1995. Identification of a novel nuclear pore-associated protein as a functional target of the HIV-1 Rev protein in yeast. *Cell* **82**:495–506.

[131] Svitkin, Y. V., A. Pause, and N. Sonenberg. 1994. La autoantigen alleviates translational repression by the 5′ leader sequence of the human immunodeficiency virus type 1 mRNA. *J. Virol*. **68**;7001–7007.

[132] Swaffield, J., J. Bromberg, and S. A. Johnston. 1992. Alterations in a yeast protein resembling HIV Tat-binding protein relieve requirement for an acidic activation in GAL4. *Nature* **357**:698–700.

[133] Szebeni, A., J. E. Herrera, and M. O. Olson. 1995. Interaction of nucleolar protein B23 with peptides related to nuclear localization signals. *Biochemistry* **34**:8037–8042.

[134] Tange, T. O., T. H. Jensen, and J. Kjems. 1996. *In vitro* interaction between human immunodeficiency virus type 1 Rev protein and splicing factor ASF/SF2-associated protein, p32. *J. Biol. Chem*. **271**:10066–10072.

[135] Usheva, A., and T. Shenk. 1994. TATA-binding protein-independent initiation: YY1, TFIIB, and RNA polymerase II direct basal transcription on supercoiled template DNA. *Cell* **76**:1115–1121.

[136] Vaishnav, Y. N., M. Vaishnav, and F. Wong-Staal. 1991. Identification of a nuclear factor that specifically binds to the Rev-responsive element (RRE) of human immunodeficiency virus type 1. *New Biologist* **3**:142–150.

[137] vanStraaten, F., R. Mueller, T. Curran, C. P. vanBeveren, and I. M. Verma. 1983. Complete nucleotide sequence of a human c-onc gene: deduced amno acid sequence of the human c-fos protein. *Proc. Natl. Acad. Sci. USA* **80**:3183–3187.

[138] Vogel, B., S.-J. Lee, A. Hildebrand, W. Craig, M. Pierschbacher, F. Wong-Staal, and E. Ruoslahti. 1993. A novel integrin specificity exemplified by binding of the avb5 integrin to the basic domain of the HIV tat protein and vitronectin. *J. Cell Biol*. **121**:461–468.

[139] Wang, Z., G. F. Morris, A. P. Rice, W. Xiong, and C. B. Morris. 1996. Wild-type and transactivation-defective mutants of human immunodeficiency virus type 1 Tat protein bind human TATA-binding protein *in vitro*. *J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol*. **12**:128–138.

[140] Waterman, M. L., and K. A. Jones. 1990. Purification of TCF-1a, a T-cell-specific transcription factor that activates the T-cell receptor Ca gene enhancer in a context-dependent manner. *New Biol*. **2**:621–636.

[141] Week, B., K. Desai, P. Loewenstein, M. Klotman, P. Klotman, M. Green, and H. K. Kleinman. 1993. Identification of a novel cell attachment domain in the HIV-1 Tat protein and its 90-kDa cell surface binding protein. *J. Biol. Chem*. **268**:5279–5284.

[142] Wen, W., J. L. Meinkoth, R. Y. Tsien, and S. S. Taylor. 1995. Identification of a signal for rapid export of proteins from the nucleus. *Cell* **82**:463–473.

[143] Westendorp, M. O., M. Li-Weber, R. W. Frank, and P. H. Krammer. 1994. Human immunodeficiency virus type 1 Tat upregulates interleukin-2 secretion in activated T cells. *J. Virol*. **68**:4177–4185.

[144] Wu, F., J. Garcia, D. Sigman, and R. Gaynor. 1991. tat regulates binding of the human immunodeficiency virus trans-activating region RNA loop-binding protein TRP-185. *Genes Dev*. **5**:2128–2140.

[145] Wu-Baer, F., W. S. Lane, and R. B. Gaynor. 1996. Identification of a group of cellular cofactors that stimulate the binding of RNA polymerase II and TRP-185 to human immunodeficiency virus 1 TAR RNA. *J. Biol. Chem*. **271**:4201–4208.

[146] Wu-Baer, F., D. Sigman, and R. B. Gaynor. 1995. Specific binding of RNA polymerase II to the human immunodeficiency virus trans-activating region RNA is regulated by cellular cofactors and Tat. *Proc. Natl. Acad. Sci. USA* **92**:7153–7157.

[147] Xu, Y., T. R. Reddy, W. H. Fischer, and F. Wong-Staal. 1996. A novel hnRNP specifically interacts with HIV-1 RRE RNA. *J. Biomed. Sci* **3**:82–91.

[148] Yaseen, N. R., B. Maizel, F. Wang, and S. Sharma. 1993. Comparative analysis of NFAT (nuclear factor of activated T cells) complex in human T and B lymphocytes. *J. Biol. Chem*. **268**:14285–14293.

[149] Yoon, J.-B., G. Li, and R. Roeder. 1994. Characterization of a familyh of related cellular transcription factors which can modualte human immunodeficiency virus type 1 transcription *in vitro*. *Mol. Cell. Biol*. **14**:1776–1785.

[150] Zauli, G., D. Gibellini, A. Caputo, A. Bassini, M. Negrini, M. Monne, M. Mazzoni, and S. Capitani. 1995. The human immunodeficiency virus type-1 Tat protein upregulates Bcl-2 gene expression in Jurkat T-cell lines and primary peripheral blood mononuclear cells. *Blood* **86**:3823–3834.

[151] Zauli, G., M. Previati, E. Caramelli, A. Bassini, E. Falcieri, D. Gibellini, L. Bertolaso, D. Bosco, I. Robuffo, and S. Capitani. 1995. Exogenous human immunodeficiency virus type-1 Tat protein selectively stimulates a phosphatidylinositol-specific phospholipase C nuclear pathway in the Jurkat T cell line. *Eur. J. Immunol*. **25**:2695–2700.

[152] Zhou, Q., and P. A. Sharp. 1996. Tat-SF1: Cofactor for stimulation of transcriptional elongation by HIV-1 Tat. *Science* **274**:605–609.

[153] Zimmermann, K., M. Dobrovnik, C. Ballaun, D. Bevec, J. Hauber, and E. Bohnlein. 1991. trans-Activation of the HIV-1 LTR by the HIV-1 Tat and HTLV-I Tax proteins is mediated by different cis-acting sequences. *Virology* **182**:874–878.